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Premature Discontinuation of Pediatric Randomized Controlled Trials: A Retrospective Cohort Study

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Abbreviations:

RCT, randomized controlled

trial REC, research ethics

committee

OR, odds ratio

CI, confidence interval

Abstract

OBJECTIVES To determine the proportion of pediatric Randomized Controlled Trials (RCTs) that are prematurely discontinued, the reasons for discontinuation, and to compare the risk for recruitment failure between pediatric and adult RCTs.

STUDY design Retrospective cohort of RCTs approved by one of six research ethics committees (RECs) in Switzerland, Germany, and Canada between 2000 and 2003. We recorded trial characteristics, trial discontinuation, and reasons for discontinuation from protocols, corresponding publications, REC files, and a survey of trialists.

RESULTS We included 894 RCTs, of which 86 enrolled children and 808 adults. Forty percent of the pediatric and 29% of the adult RCTs were discontinued. Slow recruitment accounted for 56% of pediatric and 43% of adult RCT discontinuations. Multivariable logistic regression analyses suggested that pediatric RCT was not an independent risk factor for recruitment failure after adjustment for other potential risk factors (adjusted OR 1.22, 95% CI 0.57 to 2.63). Independent risk factors were acute care setting (adjusted OR 4.00, 95% CI, 1.72 to 9.31), non-industry sponsorship (adjusted OR 4.45, 95% CI, 2.59 to 7.65) and smaller planned sample size (adjusted OR 1.05, 95% CI 1.01 - 1.09, in decrements of 100 participants).

CONCLUSION Forty percent of pediatric RCTs were prematurely discontinued, predominately due to slow recruitment. Enrollment of children was not an independent risk factor for recruitment failure.

Keywords: randomized controlled trials as a topic (MeSH); early termination of clinical trials (MeSH); pediatrics (MeSH); risk factors (MeSH)

Randomized controlled trials (RCTs) involving children are rare compared with trials of adults,(1-5) in part due to lack of funding.(4, 6) In addition, pediatric trials may be at particularly high risk for premature trial discontinuation. First, recruitment of children involves specific challenges;(7-9) The informed consent process is more complex (7) and may be affected by the reservations and skepticism of parents (who usually have to provide consent for their children) or pediatricians.(10-15) Second, compared with adult trials, rules for stopping a pediatric trial for benefit, harm, or futility may be stricter and therefore further increase the risk for early discontinuation.

On the other hand, a report of the United Kingdom Children's Cancer Study Group has suggested that pediatric trials recruit more successfully than adult trials,(16) potentially as a result of the highly collaborative network of pediatric oncology centers.(17) Other qualitative studies have found that parents are less skeptical about having their child participate in clinical trials than one might anticipate.(14, 18) Therefore, recruitment failure may be no higher - or perhaps even lower - for pediatric trials compared with adult trials.

Few empirical data exist about the actual risk of premature trial discontinuation in pediatrics. In a survey of 110 published pediatric RCTs, 32 were discontinued overall, 8 for slow recruitment, 7 for futility, 6 for efficacy, 6 for harm, and 5 for other reasons.(19, 20) Another survey of cardiovascular studies registered in ClinicalTrials.gov suggested that 65 of 782 (8%) pediatric studies were prematurely discontinued. These data, however, originate from published or registered trials and may not be representative of all initiated trials; many discontinued trials remain unpublished (21) or fail to acknowledge discontinuation in trial registries.(22)

We analyzed an international cohort of RCTs approved by six research ethics committees (RECs) in three countries to determine the risk of trial discontinuation in pediatric trials and to compare the risk for trial discontinuation specifically due to slow recruitment between pediatric and adult trials.

Methods

Previous publications have described the rationale and design of this international cohort study,(21, 23) and we presented parts of the regression analysis previously in the context of acute care RCTs.(24) In brief, we included RCTs approved between 2000 and 2003 by six research ethics committees (RECs) in Switzerland (Basel, Lucerne, Zurich, and Lausanne), Germany (Freiburg), and Canada (Hamilton). Each REC was responsible for human research in large university centers and hospitals in their respective catchment areas. All RECs had pediatric units in their catchment area and approved pediatric trials. We approached the RECs through existing contacts and, to minimize the number of ongoing or unpublished RCTs, focused on protocols that had been approved more than ten years ago.

For this analysis, we excluded protocols of RCTs that involved only healthy volunteers, were never started, or were reported as ongoing as of April 2013 (**Figure**). The participating RECs approved our study or explicitly stated that no formal ethical approval was necessary.

Definitions

We classified an RCT as pediatric if more than 50% of enrolled patients were younger than 18 years. The rationale for this inclusive threshold was that trials with more than 50% children are likely to be affected by pediatric-specific challenges.

We considered an RCT discontinued if the investigators indicated trial discontinuation in correspondence with RECs, in journal publications, or in their response to our survey (see below). If still unclear, we compared the final sample size with the planned sample size; we classified a trial as discontinued if the final sample size was $\leq 90\%$ of the planned sample size.⁽²³⁾ If the planned or final sample size was unclear, we classified the trial status as unclear. In addition, we recorded reasons for trial discontinuation.

Data Sources and Abstraction

Reviewers trained in trial methodology abstracted 30% of RCT protocols independently and in duplicate using pre-tested forms with detailed written instructions, and following formal calibration exercises with all data abstractors. Disagreements arising in duplicate review were resolved by discussion. Single investigators abstracted the remaining RCT protocols, with periodic duplicate agreement checks from a random sample of protocols at several points during the process.

We followed-up on the completion status and publication history of RCTs as of April 27, 2013, by using information from REC files and by conducting comprehensive searches for corresponding publications in electronic databases and trial registries.⁽²³⁾ If trial completion or publication status remained unclear, we surveyed the investigator by sending them a standardized questionnaire through the overseeing REC. We extracted data from all corresponding publications independently and in duplicate and resolved disagreements by consensus or third party adjudication.

Statistical Analyses

We present trial characteristics, discontinuation, and publication status as frequencies and percentages stratified by pediatric / adult.

To determine the prevalence of pediatric trials in the overall cohort, we excluded RCTs that were approved in Zurich where we had selective access to pediatric and surgical trials only. To determine

the proportion of discontinued pediatric trials, we considered RCTs from all centers and excluded RCTs with unclear completion status assuming that these RCTs were missing at random.

We used complete case multivariable logistic regression analysis to investigate the association between enrollment of pediatric versus adult patients (independent variable) and trial discontinuation due to slow recruitment.(23) We limited our regression analysis to trials that were either completed or discontinued due to slow recruitment. We additionally excluded pilot trials (4 pediatric, 47 adult) and cluster trials (2 pediatric, 6 adult) for which we expected different recruitment mechanisms. Independent variables were pediatric (vs. adult) patients, investigator sponsorship (vs. industry), sample size (as planned, continuous variable), multi-center (vs. single-center), cross-over design (vs. parallel), active control (vs. placebo or non-active intervention), reported method to predict recruitment rate (vs. no method reported), logistical support from a contract research organization or clinical trial unit (vs. no support reported), and acute care (including emergency and intensive care vs. non-acute care). The study protocol provides rationales for the chosen variables.(23) The event-to-variable ratio was 10 (90 trials discontinued due to slow recruitment and 9 explanatory variables). We conducted sensitivity analyses using multiple imputations for missing information about trial discontinuation (15). We considered 2-tailed $p \leq 0.05$ values statistically significant.

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Motivated by reports that pediatric oncology RCTs may be at lower risk for early stopping versus adult trials,(16, 17, 25) we further explored whether pediatric oncology RCTs differed from other pediatric RCTs in terms of their rate of premature discontinuation. For this analysis, we did not adjust for other potential risk factors due to the limited power.

Results

Classification and Prevalence of Pediatric Trials

We included 894 RCTs of which we classified 86 (10%) as pediatric and 808 as adult RCTs (**Figure**). Thirty-three trials included a mixed-age population of which we classified 9 as pediatric because the proportion of children younger than 18 years was over 50%. All 9 trials focused on conditions that typically manifest in childhood (i.e. 4 pediatric tumors, 2 cerebral palsy, 2 cystic fibrosis, 1 type 1 diabetes). After excluding the 43 trials approved in Zürich, the proportion of pediatric trials in the remaining five RECs was 53/851 (6%) (**Table I; available at www.jpeds.com**).

Trial Characteristics

Most pediatric trials were multicenter, investigator-initiated trials and enrolled children of various age groups (**Table II**). Compared with adult trials, pediatric trials were more frequently conducted in the acute care setting (15% versus 6%), were less frequently sponsored by industry (44% vs. 63%), and more frequently piloted their informed consent process (7% versus 1%).

Trial Discontinuation

We determined trial discontinuation from the publication alone (61/249, 25%), the survey alone (69/249, 28%, response rate 80%), REC files alone (67/249, 27%), combined sources (27/249, 11%), or recruiting less than 90% of the target sample (25/249, 10%, including 5 pediatric trials) (23). Of the 894 included RCTs, 575 (64%) were completed, 249 (28%) were discontinued prior to enrolling their target sample size, and the completion status was unclear in 70 RCTs (8%) (**Table III**).

Of the 80 pediatric RCTs with known status, 32 (40%) were discontinued. Of the 711 adult RCTs with known recruitment status, 217 (29%) were discontinued. Slow recruitment was the most frequent reason for discontinuation in both pediatric (15/27, 56%) and adult (85/197, 43%) RCTs

(**Table III**). The difference was significant in the unadjusted logistic regression model (odds ratio, OR, 1.95, 95% confidence interval, CI, 1.00 - 3.81) but not after adjustment for other potential risk factors (OR 1.22, 95% CI 0.57 – 2.63). Independent risk factors for trial discontinuation due to slow recruitment were investigator (non-industry) sponsorship (adjusted OR 4.45, 95% CI 2.59 - 7.65), acute care setting (adjusted OR 4.00, 95% CI 1.72 – 9.31), and smaller planned sample size (adjusted OR 1.05, 95% CI 1.01 – 1.09, in decrements of 100, **Table IV**). The results were robust to sensitivity analyses using multiple imputations for missing data.(24)

None of nine pediatric cancer trials was discontinued due to slow recruitment (**Table V**; available at www.jpeds.com).

Trial Publication and Reporting of Discontinuation

After a median follow-up of 11.6 years from REC approval, 46 (53%) of the 86 pediatric trials were published as a peer-reviewed journal article (14 in pediatric journals, 23 in other specialty journals, and 9 in general medical or surgical journals), and another 8 (9%) as abstracts only. We could not identify any publications corresponding to the remaining 32 (37%) REC-approved trial protocols. The respective proportions in the 808 adult RCTs were 484 (60%) published in a peer-reviewed journal, 48 (6%) published as abstracts, and 276 (34%) not published (**Table VI**).

Of the 32 discontinued pediatric trials, 12 (38%) were published as a peer-reviewed journal article of which 5 explicitly reported that their trial had stopped early.

Discussion

In an international cohort of 894 RCTs, 86 enrolled 50% or more children. Of these, 40% were discontinued prematurely. The main reason for trial discontinuation was slow recruitment. Overall, the risk for discontinuation due to slow recruitment was higher in pediatric than in adult trials. However, multivariable logistic regression analysis suggested that the pediatric setting is not an independent risk factor. Instead, higher risk for discontinuation due to slow recruitment was associated with investigator-sponsorship (non-industry), acute care setting (e.g. newborn intensive care), and smaller planned sample size of RCTs.

Strengths of our study include collaboration with six RECs from three countries to document the history of 894 RCTs that received REC approval during a three-year period. We had full access to all REC files and successfully contacted 80% of the authors to clarify whether their trial was stopped early, and why. We involved trained methodologists to identify eligible studies and to collect data. To minimize associations due to chance alone, we considered only a limited number of variables in our statistical model and conducted sensitivity analyses using multiple imputations for missing data.

Our study is limited by the reporting quality of the original RCT protocols and reports, which did not always report information regarding trial discontinuation. We used single data extraction for almost 70% of protocols, thereby potentially increasing extraction errors. However, we used pre-piloted extraction forms with detailed written instructions, conducted formal calibration exercises with all data extractors, and checked extractions from a random sample of protocols at several points during the process. Agreement was excellent with only 2 discrepancies in answers to 30 main questions of the extraction form among 270 protocols extracted in duplicate. In addition, a second investigator verified all outcome data on discontinuation and publication of RCTs.

Our findings are based on protocols that were approved more than 10 years ago. Data from more recently initiated trials are not available but might differ. Advances in standards for RCT planning (26) and understanding of the recruitment process (27) might help to reduce the high proportion of discontinued pediatric trials. It is unlikely, however, that the main risk factors for recruitment failure have substantially changed over time. Although collaborating with six RECs in three countries increases the generalizability of our results, findings may not be transferable to RCTs performed in other jurisdictions, such as in developing countries, where unique trial completion challenges exist.

A prior analysis of why pediatric RCTs are discontinued attributed only 25% (8/32) to slow recruitment.(19, 20) In our sample, slow recruitment was the main cause of early discontinuation in 56% (15/32). The difference may result from the fact that the prior analysis was based on published RCTs only. However, many discontinued RCTs are never published or, if published, fail to acknowledge slow recruitment.(21) We addressed this limitation by evaluating REC files and directly surveying trialists.

Our findings suggest that pediatric trials are at particularly high risk of recruitment failure (40%), which is concerning, especially because there are already many fewer pediatric trials with major gaps in the RCT-informed clinical evidence base.(1) Our risk factor analysis, however, should prove encouraging to pediatric trialists in that enrolment of children is not an independent risk factor for slow recruitment. Rather, recruitment in pediatric trials was associated with the same risk factors as RCTs in adults: Non-industry sponsorship may represent insufficient funding and lack of professional planning and conduct, and acute care settings often imply that substitute decision makers and caregivers are reluctant to make decisions about trial participation under time pressure. The link between small sample size and recruitment failure is less clear. Larger sample size might be a marker for RCTs conducted in research networks or in more prevalent diseases. Those RCTs might be better organized from the outset and established networks around experienced investigators might

be better able to respond to recruitment challenges. Diseases in children often have a low prevalence and may therefore implicitly constitute a particular recruitment challenge.

Our results support previous observations that pediatric cancer trials seem to be less affected by recruitment problems.(16) None of the nine pediatric cancer trials in our sample was discontinued due to slow recruitment. The apparent success of pediatric oncology trials may be the result of well-established national and international networks, and integration of the trial protocols into routine clinical care. Investigators designing trials for adult patients may therefore consider the cooperative research culture in pediatric oncology as a model.(17, 25) The next step may be careful estimation of the expected recruitment performance, which is often overestimated.(27, 28) Unless reliable and easily applicable prediction models are available,(29) pilot trials that apply the full recruitment protocol are critical to test recruitment performance and identify important barriers such as lack of eligible patients, doubt among recruiting physicians regarding equipoise, or complex protocols.(27) In our sample, only 7% of pediatric trials protocols mentioned a feasibility study. Finally, active monitoring of recruitment and proactive implementation of strategies to bolster recruitment when necessary might be crucial once RCTs are underway.(30, 31)

More than a third of pediatric RCTs were prematurely discontinued, primarily due to slow recruitment. Investigators who plan to enroll children in an RCT should consider measures to mitigate slow recruitment, especially if the trial is conducted in the acute care setting, lacks industry-partnership, and has a small sample size.

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Figure 1, Study Selection

Abbreviations: REC, Research ethics committee; RCT, randomized controlled trial

Table 1: Proportion of Pediatric Trials by Research Ethics Committee

	Zürich n=43^a	Not Zürich n=851	Basel n=221	Freiburg n=272	Lausanne n=149	Lucerne n=31	Hamilton n=178
Pediatric	33 (78%)	53 (6%)	5 (2%)	23 (8%)	5 (3%)	5 (16%)	15 (8%)
Adult	10 (22%)	798 (94%)	216 (97%)	249 (92%)	144 (97%)	26 (84%)	163 (92%)

^a In Zurich, we selectively included pediatric and surgical trials only

Table 2: Characteristics of included trials. Values are frequencies (column percentages in brackets)

	Pediatric RCTs		Adult RCTs	
	n=86		n=808	
Age group				
Unborn / preterm/newborn (0 years)	15	(17%)		
Infant / toddler (e.g. 0 to 3 years)	10	(12%)		
Primary school (e.g. 4 to 11 years)	2	(2%)		
Adolescent (e.g. 12 to 17 years)	8	(9%)		
Mix primary school / adolescent (e.g. 6 to 17 years)	12	(14%)		
Broad mix (e.g. 1 to 21 years)	39	(45%)		
Research ethics committee				
Basel	5	(6%)	216	(27%)
Hamilton	15	(17%)	163	(20%)
Freiburg	23	(27%)	249	(31%)
Lausanne	5	(6%)	144	(18%)
Zürich ^a	33	(38%)	10	(1%)
Lucerne	5	(6%)	26	(3%)
Acute care (emergency or intensive care)	13	(15%)	51	(6%)
Oncology	10	(12%)	171	(21%)
Industry sponsorship	38	(44%)	513	(63%)
Drug intervention (in one or more arms)	70	(81%)	676	(84%)

Planned target sample size, median (IQR)	200 (80, 447)	275 (103, 630)
Planned centers		
Multiple	67 (78%)	674 (83%)
Single	18 (21%)	131 (16%)
Unclear	1 (1%)	3 (0%)
Unit of randomization		
Individuals	84 (98%)	795 (98%)
Clusters	2 (2%)	10 (1%)
Body parts	0 (0%)	30 (4%)
Study design		
Parallel	81 (94%)	755 (93%)
Cross-over	4 (5%)	37 (5%)
Factorial	1 (1%)	14 (2%)
Unclear	0 (0%)	2 (0%)
Study purpose		
Superiority	57 (66%)	595 (74%)
Non-inferiority	19 (22%)	120 (15%)
Unclear	10 (12%)	93 (12%)
Labeled as pilot RCT	5 (6%)	64 (8%)
Comparison group(s)		
Included placebo or no treatment (often add-on RCTs)	50 (58%)	483 (60%)
Active comparator(s) only	36 (42%)	325 (40%)
Data Safety and Monitoring Board mentioned	18 (21%)	239 (30%)

Method to predict recruitment rate mentioned	21	24%	60	7%
Pilot study including informed consent	6	(7%)	5	(1%)
Reported methodological/logistical support	31	(36%)	355	(44%)

Abbreviations: RCT, randomized controlled trial; IQR, inter-quartile range

^a In Zurich, we selectively included pediatric and surgical trials only

Table 3: Prevalence of trial discontinuation and reported reasons for discontinuation. Values are frequencies (column percentages in brackets)

	Pediatric RCTs		Adult RCTs	
	n=86		n=808	
Completion status				
Completed	48	(56%)	527	(65%)
Discontinued	32	(37%)	217	(27%)
Unclear	6	(7%)	64	(8%)
Reason for discontinuation				
Slow recruitment	15	(19%)	85	(11%)
Futility	4	(5%)	33	(4%)
Benefit / harm	5	(6%)	28	(4%)
Other ^a	2	(3%)	47	(6%)
Unknown reason	5	(6%)	20	(2%)

Abbreviations: RCT, randomized controlled trial

^a such as administrative, strategic, or financial

Table 4: Risk factors for discontinuation due to slow recruitment, multivariable logistic regression

Protocol characteristics	Discontinued due	Completed n=526 ^a	Univariable effect		Multivariable effect	
	to slow recruitment n=90 ^a		OR (95% CI)	P	Adjusted OR (95% CI)	P
Pediatric RCT (vs. adult)	13 (14%)	44 (8%)	1.95 (1.00-3.81)	0.049	1.22 (0.57-2.63)	0.61
Acute care RCT (vs. non-acute care)	12 (13%)	27 (5%)	2.97 (1.44-6.14)	0.003	4.00 (1.72-9.31)	0.002
Investigator sponsorship (vs. industry)	59 (66%)	158 (30%)	4.43 (2.76-7.12)	<0.001	4.45 (2.59-7.65)	<0.001
Smaller planned sample size, median (IQR)	180 (80-320)	364 (155-800)	1.06 (1.01-1.11) ^b	0.010	1.05 (1.01-1.09) ^b	<0.001
Multi-center status (vs. single-center)	71 (79%)	470 (89%)	0.46 (0.26-0.84)	0.011	1.80 (0.85-3.82)	0.12
No methodological/ logistical support reported (vs. reported)	62 (69%)	279 (53%)	1.94 (1.2-3.14)	0.007	1.49 (0.86-2.56)	0.088
Active control (vs. placebo / no active control)	37 (41%)	204 (39%)	1.14 (0.72-1.79)	0.58	1.37 (0.83-2.24)	0.22
Cross-over design (vs. parallel)	8 (9%)	21 (4%)	2.61 (1.11-6.17)	0.028	2.18 (0.82-5.79)	0.13
No method to predict recruitment reported (vs. reported)	78 (87%)	486 (92%)	0.53 (0.27-1.06)	0.073	1.15 (0.52-2.54)	0.74

Abbreviations: OR, odds ratio; CI, confidence interval; RCT, randomized controlled trial; IQR, inter-quartile range

^a We limited the analysis to RCTs discontinued for slow recruitment and completed RCTs and excluded 51 pilot RCTs, and 8 RCTs that randomized clusters (see Methods for rationale). We excluded 71 RCTs with missing discontinuation information, 25 RCTs with missing reasons for discontinuation, and 12 RCTs with missing sample size information.

^b in decrements of 100 patients

Table 5: Comparison of Pediatric Cancer Trials with Non-Cancer Trials and Adult Trials

	Pediatric cancer trials^a n=9	Pediatric non-cancer trials^a n=48	Adult cancer trials^a n=117
Completed	9 (100%)	35 (73%)	98 (84%)
Discontinued due to slow recruitment	0	13 (27%)	19 (16%)

^a Same sample as used for multivariable regression, see legend of Table 4

Table 6: Publication of Included Trials

Publication type	Pediatric RCTs		Adult RCTs	
	n=86		n=808	
Peer-reviewed journal	46	(53%)	484	(60%)
Abstract / letter / other	8	(9%)	48	(6%)
Not published	32	(37%)	276	(34%)